NInChI Commentary

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Results of Terminology Efforts

Start	# Terms	Final	# Terms	# Added	# Same	%-Same
ASTM	78	E2456-06	15	7	8	10
PAS 71	152	TS 27687	12	3	9	6
PAS 71	152	TS 80004-1	14	7	7	5
PAS 131	51	TS 80004-7	12	10	2	4
PAS 132	77	TS 80004-5	6	6	0	0
PAS 134	91	TS 80004-4	28	16	12	13

Colleagues thought they were complete, but terms added.

[Applied to my suggested carbon nanotube NInCHI: started with 37 keystrokes –subtracted 4 added 14 yielding 84% same.]

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Regulatory Policy and Tools

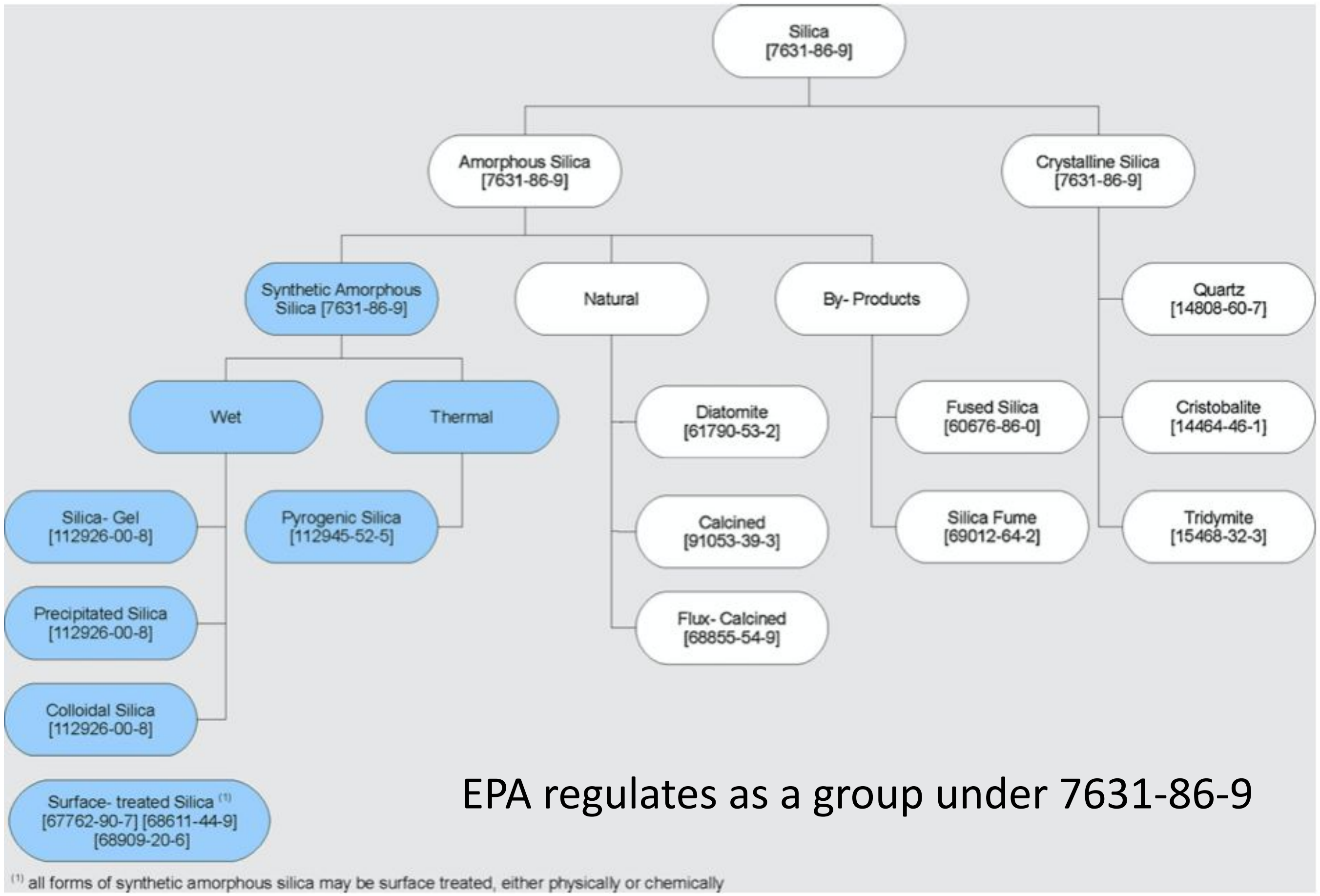
Lynch *et al.* state:

- all forms of silica have the same CAS RN;
- CAS uses an unsystematic way to assign RNs; and
- Differentiates 'substance' from 'compound.'

For EPA:

- 'chemical substance'' means any organic or inorganic substance of a particular molecular identity & mixtures of those
- Molecular identity does not differentiate states (gas, liquid and solid) or connectivity
- Administrative rules are used to fill gaps, e.g. chemical categories such as poorly soluble low toxicity
- Their experience is with molecules, not solids, which were grandfathered onto TSCA

Silica Industry View of Types & CAS RNs



EPA regulates as a group under 7631-86-9

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EPA Tools for Registration

Unable to insist on toxicity data and needing to respond within 90 days on a submission, the EPA developed tools:

- Chemical categories;
- SARs, QSARs for selected species, e.g. fathead minnow;
- Standardized test methods & GLP (prevent fraud); and
- Exceptions to molecular identity grouping, e.g. respiratory limits.

REACH is in the process of adopting tools as it is facing the inability to insist on toxicity testing

Suggestion

NInChI notation and 'human interpretability' should anticipate the tools, not the policy framework

- Composition (as molecular & particle structures), size and crystallinity align with the **S** in **QSAR**
- Composition (as ligands, dissolution products and ROS generation), morphology and size align with the **A** in **QSAR**

This approach would be:

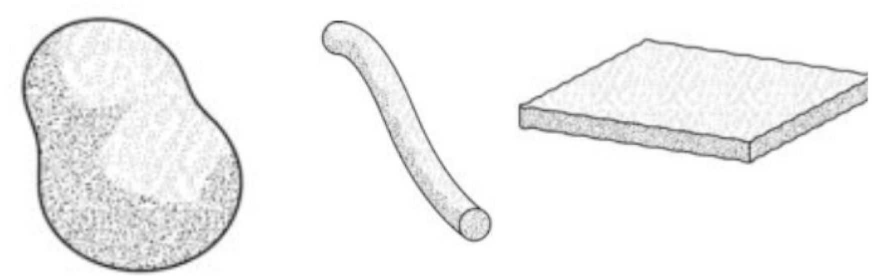
- Most visible with particle morphology and differentiating connectivity in solids and ligands
- A challenge to having unique representations

Dimension & Shape

Number of Dimensions	Material Sciences Degrees of Freedom	Geometry	TC-229 Constrained
0	Sphere	Point	-
1	Rod/Tube	Line	Plate
2	Plane	Plane	Fiber/Tube
3	Macroscale Composite	Volume	Sphere

- Elementary geometry: point, line, plane, volume
- Materials Sciences attempt to combine nanoscale entities with composite systems
- ISO shape is Cartesian coordinates using aspect ratios from toxicity (fiber *vs.* sphere)

Pictures Added to Remind Ourselves

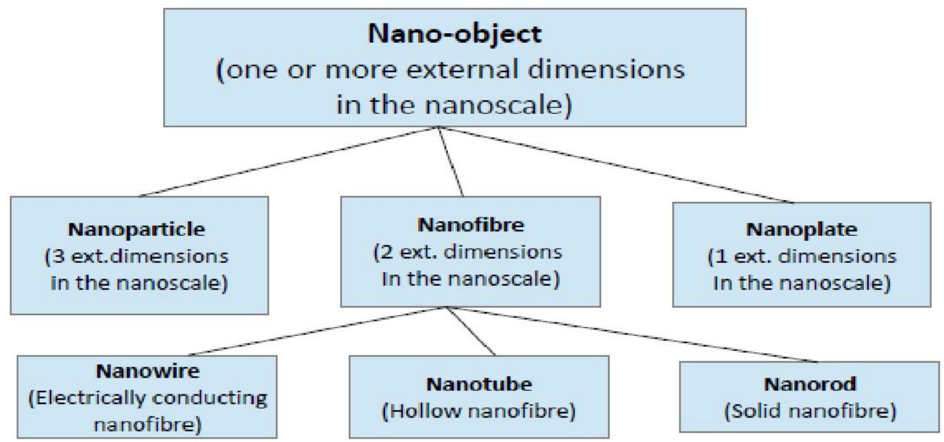


a) nanoparticle b) nanofibre c) nanoplate

Figure 1 — Schematic diagrams showing some shapes for nano-objects

- These are generic, globular shapes
- Frustrated phagocytosis due to fibers was a driving force (fiber lengthy and rigidity important)

TC-229 Hierarchy Incomplete



Reference: ISO/TS 27687:2008-08 Fragment of hierarchy of terms related to nano-objects

- Nanofibre is the generic shape with terms provided for hollow objects and functions
- Nanoparticle is the generic shape with terms like core-shell for specific particle structures
- No term for hollow spheres

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Defining Attributes

- Traditional lung inhalation dealt with residence time (dissolution, lung clearance, translocation)
- Cell entry is a ‘new’ concern:
    - May occur at sizes up to ~700 nm, which encompasses microplastics (FDA goes up to 1,000 nm for nano);
    - Cell entry and passing biological barriers are the shared concerns of toxicology & pharmacology;
    - Shape for cell entry is not the shape for functionality; and
    - Crystallinity does not affect cell entry, but influences properties (band gap & free radical generation)
- The ‘defining attributes’ come from regulators & toxicologists; properties from materials science
- Recommend using constituent particle

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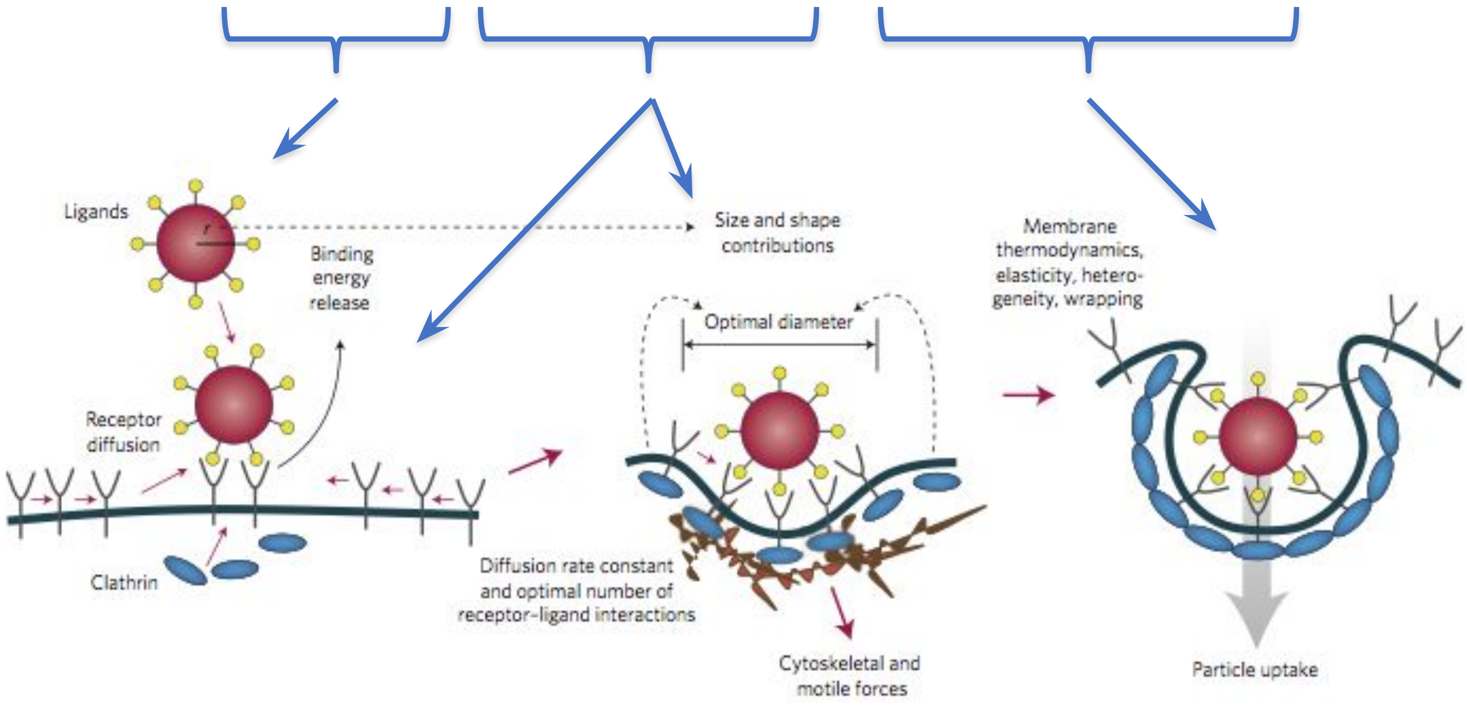
Ligands & Wrapping

Rolling Adhesion Engulfment



From Nel *et alia* 2009

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Adhering to Surfaces (PBPK Modeling)

Ligands are molecules that project into the medium affecting adhesion including targeting cell of the membrane

Ligands attach to the hydrated surface of the outwardly exposed solid

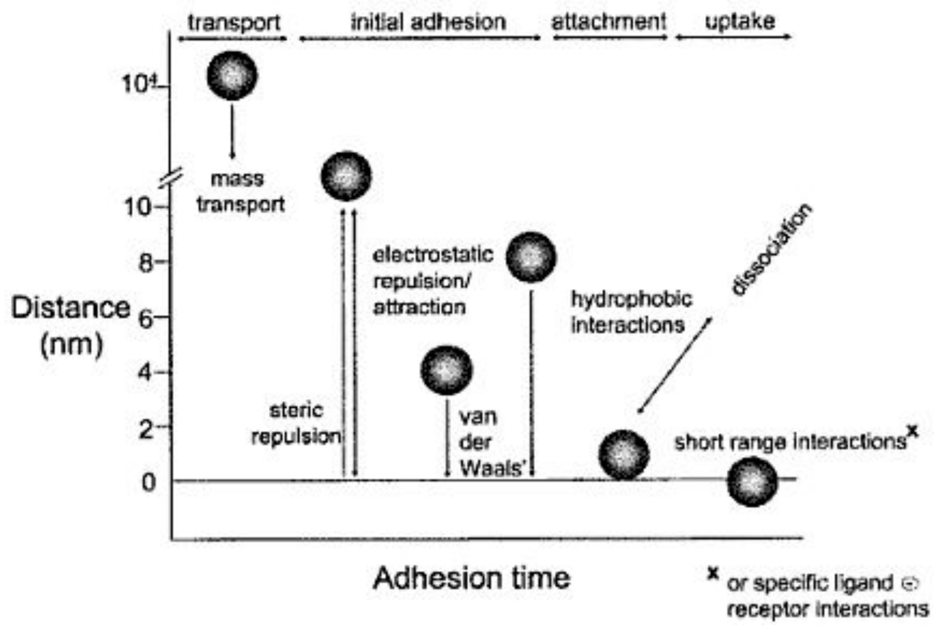


Fig. 9. Processes occurring in the deposition of nanoparticles in flow conditions as a function of the range of interaction forces (nm) and adhesion times. At the start, mass transport to the surface occurs, initial adhesion following through electrostatic attraction and van der Waals' forces. Hydrophobic interactions can play their part as well as specific receptor-ligand interactions which are short-range interactions. Drawn after Vacheethasanee and Marchant.[38]

Solids, Ligands & Properties

Solids

- Chemical reservoir for dissolution species
- Light scattering & refractive index
- Band gap & generation of free radicals

Outward solid surface

- Initial state for hydration, first step in dissolution
- Initial state for surface treatment reactions

Ligands

- Surface wetting with the liquid media
- Adhesion to surfaces, e.g. cell membranes
- Zeta potential reflects acid/base acidity
- Hydrophobic & steric interactions
- Targeting membrane species

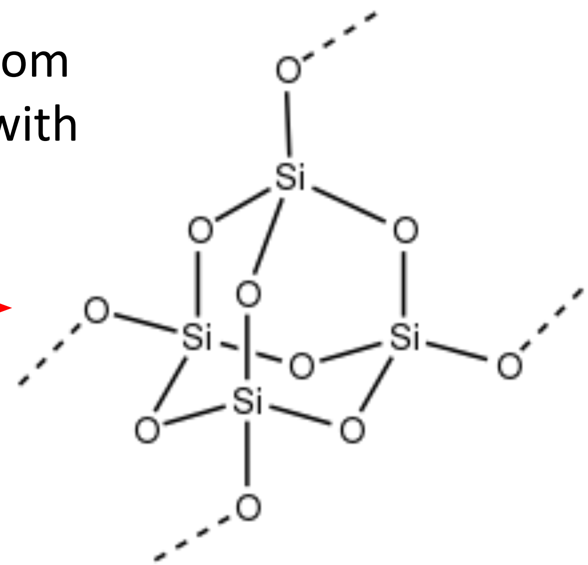
Connectivity for Solids ≠ Ligands

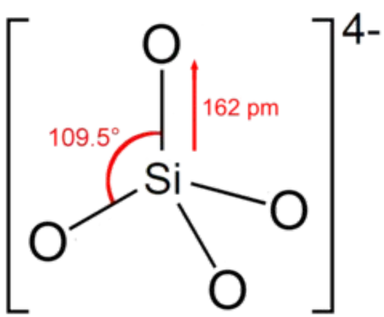
InChI=1S/O2Si/c1-3-2

This is the molecular identity

Connectivity in solids is one Si atom bonded to four oxygens shared with other silicon atoms

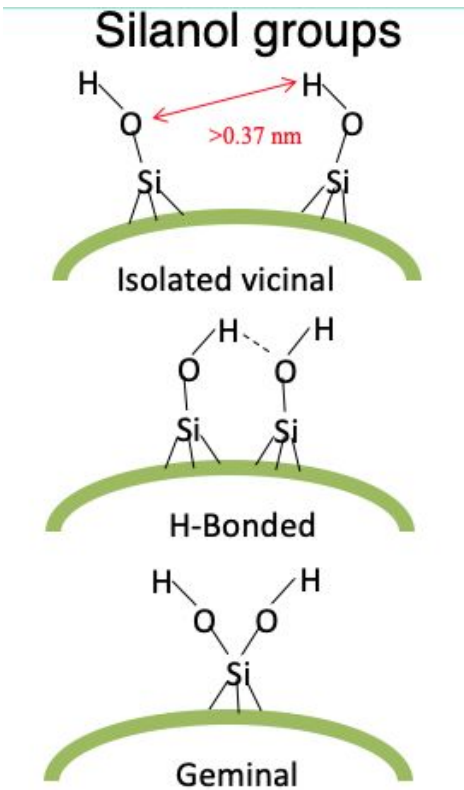
Silica

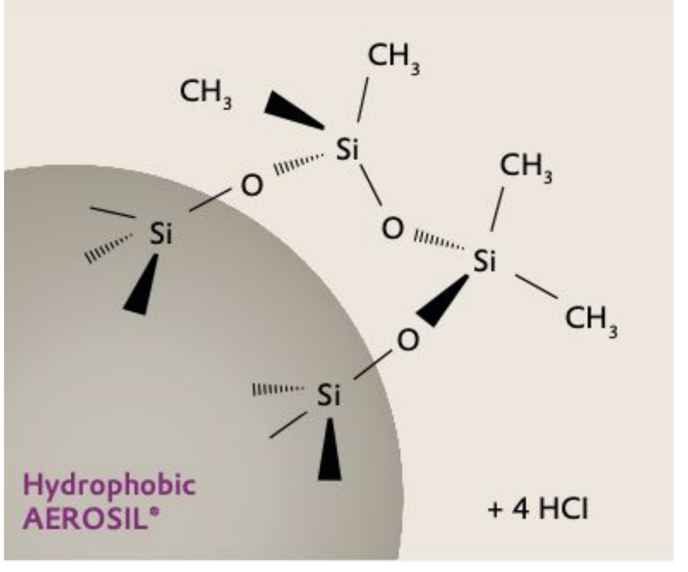




Silicate

Surface Treatment & Silanol Group Connectivity





Surface Si atoms hydrate first and some react with surface treatment

NInChI Example: carbon nanotube

- *NInChI*=0.00.1A/C/mtu/s4d-10/w(3,1)/y1
  - No length or volume corresponding to chirality
  - Tube is not a shape, it is a hollow fiber
  - Cartesian coordinates with two being the cross section of the cylinder (radius on x-axis; radius on y-axis)
  - Is chirality crystallinity? Is it connectivity?
- *NInChI*=0.00.1A/C/mfib/s2r_{xy}-10;??r_z-09/w(3,1)/y1
  - Fiber not tube, size expressed as a ray that is equal on the x- & y-axes and a ray of unknown length along the z-axis
  - The hollow space within the tube not described
  - 37 keystrokes; subtract 4; add 14 yields 84% same

NInChI Example gold (2 nm) on silica (20 nm diameter)

- *NInChI*=0.00.1A/Au/msh/s2t10r1-9;12r2-9!/O2Si/c1-3-2/msp/s20d-9/k000/y2&1
  - Shell is not a shape;
  - Components are given as molecular InChI's;
  - SiO2 size is a diameter whereas Au is a thickness;
  - No crystallinity for Au
- The primary suggestion on the next page is to express size as a distance along a ray originating at the origin. This is done already for Au with an r1 extending to an r2.

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Alternative NInChI

- *NInChI*=0.00.1A/ O2Si/c1-4-3-2/msp/s0r_{xyz}1-9;10r_{xyz}2-9/k000!/ Au/msp/s210r_{xyz}1-9;12r_{xyz}2-9/kfcc
  - The distance r_{xyz} begins at 0 and extends to 10 nm for silica; Au starts at 10 nm and extends to 12 nm.
  - Shell (msh) has been replaced by sphere (msp)
  - Rather than listing components alphabetically (by the element's symbol) with a third layer indicating spatial arrangement, one can use the origin
  - SiO2 connectivity expressed for the solid, not the molecule
  - There is no need for a third NInChI layer
- 72 keystrokes; subtract 9 add 29; same 80%

Comparing Versions

NInChI Prototype Layer

1. NInChI version (NInChI=0.00.1A)
2. Component (Substance/connectivity-as-molecule/shape/size)
   - Repeated for each component listed alphabetically
3. Spatial arrangement of components

- Suggested NInChI Layer

1. NInChI version (NInChI=0.00.1A)
2. Particle Components (Substance/connectivity-as-solid/shape/size)
   - Repeated for each component by linear distance from r1=0
3. Surface components (substance/connectivity-as-molecule)